

Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) **EP 1 099 439 A2**

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:
16.05.2001 Bulletin 2001/20

(21) Application number: **00309721.9**

(22) Date of filing: **03.11.2000**

(51) Int Cl.⁷: **A61K 31/00**, A61K 31/472,
A61K 31/454, A61K 31/4468,
A61P 3/06, A61P 3/04,
A61P 9/10
// (A61K31/472, 31:00),
(A61K31/454, 31:00),
(A61K31/4468, 31:00)

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR**
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **10.11.1999 US 164547**

(71) Applicant: **Pfizer Products Inc.**
Groton, Connecticut 06340 (US)

(72) Inventors:
• **Chandler, Charles Edward**
Kula, Maui, Hawaii 96790 (US)

• **Hickman, Mary Anne**
Groton, Connecticut 06340 (US)
• **Lundy, Kristin Marie**
Groton, Connecticut 06340 (US)
• **Morgan, Bradley Paul**
Groton, Connecticut 06340 (US)

(74) Representative:
Atkinson, Jonathan David Mark et al
Urquhart-Dykes & Lord
Tower House
Merrion Way
Leeds LS2 8PA (GB)

(54) **Use of apo B secretion/MTP inhibitors**

(57) The invention provides methods useful in reducing intestinal fat absorption in an animal, preferably a mammal including a human subject or a companion animal, which methods comprise administering to an animal in need of such reduction, an amount of an apolipoprotein B (apo B) secretion/microsomal triglyceride transfer protein (MTP) inhibitor, preferably in combination with an anti-obesity agent. The invention further provides pharmaceutical compositions comprising amounts of an apo B secretion/MTP inhibitor and an an-

ti-obesity agent, and to methods of using such compositions in reducing intestinal fat absorption in an animal, preferably a mammal including a human subject or a companion animal, in need of such reduction. The invention further provides a kit comprising an amount of an apolipoprotein B secretion/microsomal triglyceride transfer protein inhibitor and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form; an amount of an anti-obesity agent and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and a container.

EP 1 099 439 A2

Description

BACKGROUND OF THE INVENTION

[0001] Conventional therapeutic approaches to the treatment of obesity in animals, including humans and companion animals, have traditionally focused on the regulation of energy intake. However, there is now a growing awareness that, while moderation of caloric intake is initially effective in reducing body weight, such regimens are not particularly effective over the long-term. In response thereto, alternative strategies requiring less rigorous observation of caloric consumption have been developed, including the use of agents that alter the absorption of dietary fat from the gastrointestinal tract.

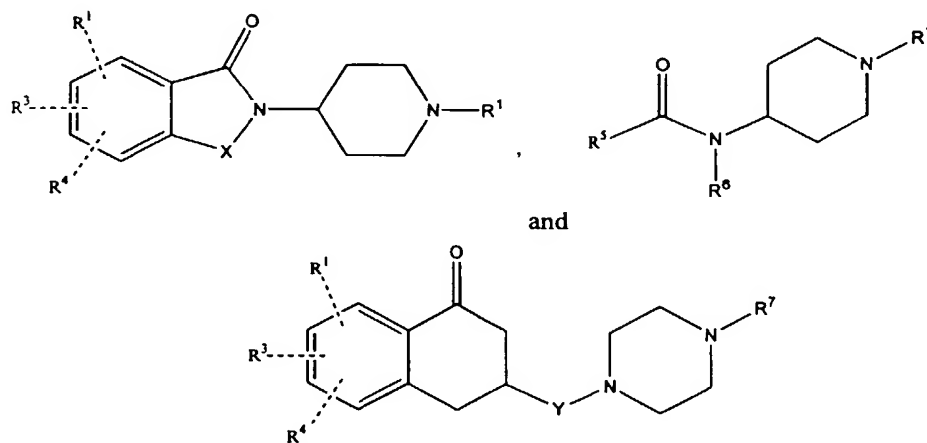
[0002] The gastrointestinal digestion and absorption of ingested lipids comprises several discrete steps. Following dispersion of bulk fat into finely emulsified droplets in the stomach, fatty acid esters are hydrolyzed enzymatically, partially by the previous action of gastric lipase in the stomach, but predominantly by pancreatic lipase in the upper small intestine. In recent years, studies concerning certain inhibitors of pancreatic lipase, orlistat for example, have indicated that the treatment of obesity with such inhibitors may hold some promise. However, in view of the complexity of the genetic component of obesity and the various psychologic factors involved in maintaining lifestyle habits, the long-term efficacy of such drugs in managing body weight and decreasing obesity-related medical complications is unknown. Accordingly, the identification of alternative therapeutic regimens remains desirable.

[0003] The instant invention provides methods and pharmaceutical compositions useful in the reduction of intestinal fat absorption in an animal, preferably a mammal including a human subject, a companion animal, or livestock, using an apolipoprotein B (apo B) secretion/microsomal triglyceride transfer protein (MTP) inhibitor, preferably in combination with an anti-obesity agent.

[0004] Microsomal triglyceride transfer protein catalyzes the transport of triglyceride, cholesteryl ester and phospholipids and has been strongly implicated as a mediator in the assembly of apo B-containing lipoproteins, biomolecules which contribute to the formation of atherosclerotic lesions. Specifically, the subcellular (lumen of the endoplasmic reticulum) and tissue distribution (liver and intestine) of MTP have led to speculation that it plays a role in the assembly of plasma lipoproteins, as these are known sites of plasma lipoprotein assembly. The ability of MTP to catalyze the transport of triglyceride between membranes is consistent with this speculation and suggests that MTP may effect the transport of triglyceride from its site of synthesis in the endoplasmic reticulum membrane to nascent lipoprotein particles within the lumen of the endoplasmic reticulum.

[0005] Compounds that inhibit apo B secretion and/or MTP are accordingly useful in the treatment of diseases and conditions in which, by inhibiting apo B secretion/MTP, serum cholesterol and triglyceride levels may be reduced. Such conditions may include, for example, hypercholesterolemia, hypertriglyceridemia, pancreatitis, atherosclerosis, diabetes and the like. For detailed discussions see, for example, Wetterau et al., *Science*, 258, 999-1001 (1992) and Wetterau et al., *Biochem. Biophys. Acta.*, 875, 610-617 (1986).

[0006] Specific examples of compounds having utility as apo B secretion/MTP inhibitors are disclosed in European patent application publication Nos. 0 584 446 A2 and 0 643 057 A1, the latter of which discloses certain compounds of the generic formulae



which have utility as inhibitors of MTP.

[0007] Furthermore, commonly assigned PCT International Application Publication Nos. WO 96/40640 and WO

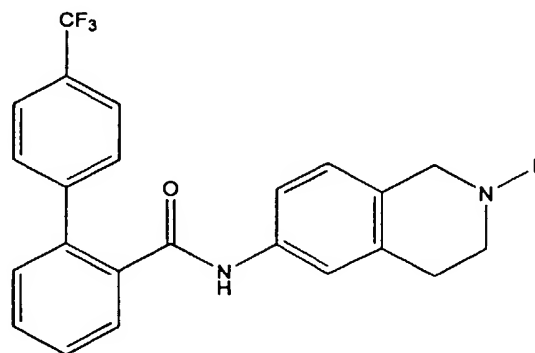
98/23593, each of which designate, *inter alia*, the United States, disclose certain tetrahydroisoquinolines having utility as apo B secretion/MTP inhibitors. Additional apo B secretion/MTP inhibitors useful in the practice of the instant invention are known, or will be apparent in light of this disclosure, to one of ordinary skill in the art.

SUMMARY OF THE INVENTION

[0008] The instant invention provides methods and pharmaceutical compositions for reducing intestinal fat absorption in an animal, preferably a mammal including a human subject, a companion animal, or livestock, which methods comprise administering to an animal in need of such reduction, an intestinal fat absorption reducing amount of an apo B secretion/MTP inhibitor, preferably in combination with an amount of an anti-obesity agent.

[0009] The invention preferably relates to methods of reducing intestinal fat absorption in an animal, preferably a mammal including a human subject, a companion animal, or livestock, which methods comprise administering to an animal in need of such reduction an apo B secretion/MTP inhibitor selected from the group consisting of:

(i) a compound of formula (I)



(I)

the stereoisomers and hydrates thereof, and the pharmaceutically acceptable salts of said compounds, stereoisomers and hydrates, wherein the functional group L is as defined in the specification hereinbelow;

(ii) the compound BMS-197636, also known as 9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof;

(iii) the compound BMS-200150, also known as 2-[1-(3,3-diphenylpropyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one, and the pharmaceutically acceptable salts thereof; and

(iv) the compound BMS-201038, also known as 9-[4-(4-[2-(4-trifluoromethylphenyl)benzoylamino]piperidin-1-yl)butyl]-N-2,2,2-trifluoroethyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof.

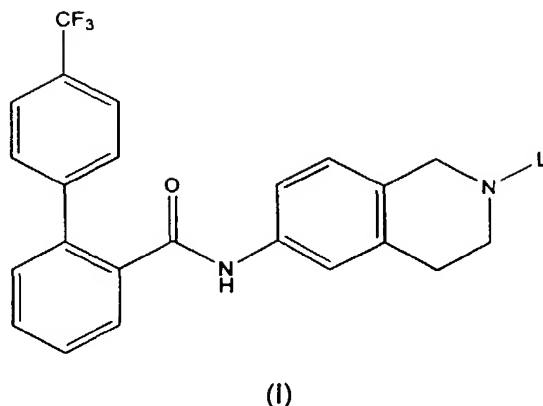
[0010] The invention further relates to pharmaceutical compositions and to methods of using such compositions in reducing intestinal fat absorption in an animal, preferably a mammal including a human subject, a companion animal, or livestock, wherein said compositions preferably comprise an apo B secretion/MTP inhibitor, a hydrate, stereoisomer thereof, or a pharmaceutically acceptable salt of said inhibitor, hydrate, or stereoisomer disclosed hereinabove in combination with an anti-obesity agent.

[0011] The invention still further relates to a kit comprising an amount of an apolipoprotein B secretion/microsomal triglyceride transfer protein inhibitor and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form; an amount of an anti-obesity agent and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and a container.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The instant invention provides methods and pharmaceutical compositions useful in reducing intestinal fat absorption in an animal, preferably a mammal including a human subject, a companion animal, or livestock, which methods comprise administering to an animal in need of such reduction an intestinal fat absorption reducing amount of an apo B secretion/MTP inhibitor, preferably a compound selected from the group consisting of:

(i) a compound of formula (I)



the stereoisomers and hydrates thereof, and the pharmaceutically acceptable salts of said compounds, stereoisomers and hydrates, wherein L represents:

(A) X-Y-Z, wherein:

X is a moiety selected from the group consisting of CH₂, CO, CS, or SO₂ ;

Y is a moiety selected from the group consisting of a direct link, aliphatic hydrocarbylene radicals having up to 20 carbon atoms, which radical may be monosubstituted by hydroxy, (C₁-C₁₀)alkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)acyloxy, or (C₆-C₁₀)aryl, NH, and O, provided that if X is CH₂, Y is a direct link; and

Z is a moiety selected from the group consisting of:

(1) hydrogen, halogen, cyano,

(2) hydroxy, (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkylthio, (C₁-C₁₀)acyl, thiophenylcarbonyl, (C₁-C₁₀)alkoxycarbonyl,

(3) (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₆-C₁₀)aryl(C₁-C₁₀)alkylamino, provided that Y is not O or NH,

(4) unsubstituted vinyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl and fused benz derivatives thereof, (C₁-C₁₀)polycycloalkyl, (C₄-C₈)cycloalkenyl, (C₇-C₁₀)polycycloalkenyl,

(5) (C₆-C₁₀)aryloxy, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryl(C₁-C₁₀)alkoxy, (C₆-C₁₀)aryl(C₁-C₁₀)alkylthio, (C₃-C₈)cycloalkyloxy, (C₄-C₈)cycloalkenyloxy,

(6) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5 to 14 ring atoms, wherein said radicals contain a total of from 1 to 4 ring heteroatoms independently selected from oxygen, nitrogen, and sulfur, and wherein the individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, provided that if X is CH₂, Z is H or is selected from groups (4) and (6),

wherein, when Z contains one or more rings, said rings may each independently bear 0 to 4 substituents independently selected from halo, hydroxy, cyano, nitro, oxo, thio, aminosulfonyl, phenyl, phenoxy, phenylthio, halophenylthio, benzyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylamino(C₁-C₁₀)alkoxy, (C₁-C₃)perfluoroalkyl, (C₁-C₃)perfluoroalkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)acyloxy, (C₁-C₁₀)acyloxy(C₁-C₁₀)alkyl, and pyrrolidinyl; or

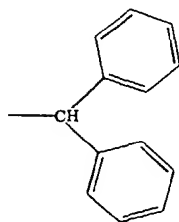
(B) G, wherein G is selected from the group consisting of:

(a) a phenyl or heterocyclic ring wherein said heterocyclic ring contains a total of from 3 to 14 ring atoms, wherein said heterocyclic ring incorporates a total of from 1 to 4 ring heteroatoms selected independently from oxygen, nitrogen, and sulfur, wherein the individual rings of said heterocyclic ring may be independently saturated, partially saturated or aromatic, and wherein each of said phenyl or heterocyclic rings may

have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acyloxy, (C₁-C₆)acylamino and (C₁-C₆)perfluoroacylamino;

(b) -CH₂CN,

(c)



(d) (C₂-C₁₂)alkyl or (C₂-C₁₂)perfluoroalkyl wherein each of said (C₂-C₁₂)alkyl and (C₂-C₁₂)perfluoroalkyl is substituted optionally with from 1-3 substituents selected independently from:

(1) phenyl, halogen, nitro, cyano, hydroxy, -NR¹R², -OCOR³, (C₁-C₄)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)thioalkoxy or (C₁-C₄)perfluorothioalkoxy,

where R¹ and R² in the definition of -NR¹R² are each selected independently from hydrogen, formyl, phenyl, benzyl, benzoyl, (C₃-C₈)cycloalkyl, (C₃-C₈)cycloalkenyl, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₆)acyl, (C₁-C₆)perfluoroacyl, aminocarbonyl, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, aminosulfonyl, (C₁-C₄)alkylaminosulfonyl, di(C₁-C₄)alkylaminosulfonyl, (C₁-C₄)perfluoroalkylaminosulfonyl, di(C₁-C₄)perfluoroalkylaminosulfonyl, (C₁-C₄)alkylsulfonyl, and (C₁-C₄)perfluoroalkylsulfonyl, or where R¹ and R², taken together with the nitrogen atom to which they are attached, form a saturated, partially-saturated or aromatic heterocyclic ring, wherein said heterocyclic ring contains a total of from 3 to 14 ring atoms and incorporates optionally an additional 1 to 4 ring heteroatoms selected independently from oxygen, nitrogen and sulfur, wherein said heterocyclic ring may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acylamino, and (C₁-C₁₀)acyloxy,

where R³ in the definition of -OCOR³ is selected from -NR¹R², phenyl, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₆)alkoxy and (C₁-C₆)perfluoroalkoxy,

(2) (C₃-C₈)cycloalkyl or (C₃-C₈)cycloalkenyl wherein each of said (C₃-C₈)cycloalkyl and (C₃-C₈)cycloalkenyl may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acylamino, (C₁-C₁₀)perfluoroacylamino, (C₁-C₁₀)acyloxy, and

(3) a saturated, partially-saturated or aromatic heterocyclic ring containing a total of from 3 to 14 ring atoms, wherein said heterocyclic ring incorporates a total of from 1 to 4 ring heteroatoms selected independently from oxygen, nitrogen and sulfur, wherein said heterocyclic ring may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acylamino, (C₁-C₁₀)perfluoroacylamino, (C₁-C₁₀)acyloxy;

(e) (C₃-C₈)cycloalkyl or (C₃-C₈)cycloalkenyl wherein each of said (C₃-C₈)cycloalkyl and (C₃-C₈)cycloalkenyl

nyl may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thio, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acylamino, (C₁-C₁₀)perfluoroacylamino, (C₁-C₁₀)acyloxy; and

(f) -(CH₂)_nCOR⁴, where R⁴ in the definition of -(CH₂)_nCOR⁴ is selected from hydroxy, phenyl, -NR¹R², (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₃-C₈)cycloalkyl, and (C₃-C₈)cycloalkenyl, where n is an integer from 1 to 4;

(ii) the compound BMS-197636, also known as 9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof;

(iii) the compound BMS-200150, also known as 2-[1-(3,3-diphenylpropyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one, and the pharmaceutically acceptable salts thereof; and

(iv) the compound BMS-201038, also known as 9-[4-(4-[2-(4-trifluoromethylphenyl)benzoylamino]piperidin-1-yl)butyl]-N-2,2,2-trifluoroethyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof.

[0013] A preferred subgroup of formula (I) compounds are those compounds selected from the group consisting of 4'-trifluoromethyl-biphenyl-2-carboxylic acid-(2--butyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide, 4'-trifluoromethyl-biphenyl-2-carboxylic acid-[2-(2-acetyl aminoethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl amide, the hydrates thereof, and the pharmaceutically acceptable salts of said compounds, and said hydrates.

[0014] A further preferred subgroup of apo B secretion/MTP inhibitors includes the compound 9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof; the compound 2-[1-(3,3-diphenylpropyl)-4-piperidinyl]-2,3-dihydro-1 H-isoindol-1-one, and the pharmaceutically acceptable salts thereof; and the compound 9-[4-(4-[2-(4-trifluoromethylphenyl)benzoylamino]piperidin-1-yl)butyl]-N-2,2,2-trifluoroethyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof.

[0015] The invention further provides methods useful in reducing intestinal fat absorption in an animal which comprise administering to an animal, preferably a mammal including a human subject, a companion animal, or livestock in need of such reduction an intestinal fat absorption reducing amount of an apo B secretion/MTP inhibitor, preferably an apo B secretion/MTP inhibitor shown and described hereinabove, and an amount of an anti-obesity agent.

[0016] The invention still further provides pharmaceutical compositions comprising amounts of an apo B secretion/MTP inhibitor, preferably an apo B secretion/MTP inhibitor shown and described hereinabove, an anti-obesity agent and, preferably, a pharmaceutically acceptable carrier, vehicle or diluent, and methods of using such compositions in reducing intestinal fat absorption in an animal, preferably a mammal including a human subject, a companion animal, or livestock, which comprise administering to an animal in need of such reduction, an intestinal fat absorption reducing amount of such composition.

[0017] The invention still further provides a kit comprising an amount of an apolipoprotein B secretion/microsomal triglyceride transfer protein inhibitor and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form; an amount of an anti-obesity agent and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and a container.

[0018] For purposes of this invention, an "animal" includes a warm-blooded animal of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds, preferably humans and companion animals such as dogs, cats and horses, and livestock such as cows, pigs, and the like.

[0019] As employed throughout the instant description and appendant claims, the term "reduction of intestinal fat absorption" means a reduction of intestinal fat absorption as evidenced by a corresponding increase in fat content of fecal matter.

[0020] The following selected functional group definitions and examples are employed throughout the instant description and appendant claims and are offered by way of illustration, and not by limitation.

[0021] The term "heterocyclyl" as employed within the definition of Z is meant to embrace any single ring or fused ring system containing at least one ring heteroatom independently selected from O, N, and S. Thus, a polycyclic fused ring system containing one or more carbocyclic fused saturated, partially unsaturated or aromatic rings (usually benz rings) is within the definition of heterocyclyl so long as the system also contains at least one fused ring which contains at least one of the aforementioned heteroatoms. As a substituent, such heterocyclyls may be attached to the remainder of the molecule from either a carbocyclic (e.g. benz) ring or from a heterocyclic ring.

[0022] The phrase "one or more rings" when employed in the definition of Z is intended to mean any (single or fused) cyclic moiety or moieties contained in Z. The rings may be carbocyclic or heterocyclic, saturated or partially unsaturated and aromatic or non-aromatic.

[0023] Reference to a fused polycyclic ring system or radical means that all rings in the system are fused.

[0024] The term "aryl", e.g. (C₆-C₁₀)aryl, when employed in the description of a substituent means the ring or substituent is carbocyclic. Aromatic moieties which contain one or more heteroatoms are included as a subset of the term "heterocyclyl" as discussed hereinabove.

[0025] The term "halogen" employed throughout the description and appendant and claims is inclusive of fluoro, chloro, bromo and iodo, unless noted otherwise.

[0026] The term "perfluoro", when used in conjunction with a specified hydrocarbon radical, is meant to include a substituent wherein the individual hydrogen atoms thereof may be substituted therefor with one or more, and preferably, from 1 to 9 fluorine atoms. Exemplary of such radicals are trifluoromethyl, pentafluoroethyl, heptafluoropropyl, and the like.

[0027] The term "acyl" when employed in the description of a substituent refers to an aliphatic or hydrocarbon moiety attached to a carbonyl group through which the substituent bonds.

[0028] Reference to the terms "alkyl" and "alkoxy" includes both straight and branched chain radicals, however, it is to be understood that references to individual radicals, for example "propyl" or "propoxy", embrace only the straight chain radical, branched chain isomers such as "isopropyl" or "isopropoxy" being referred to specifically.

[0029] The central benz-heterocyclic ring system of formula (I), i.e. the fused bicyclic ring system attached through its single ring nitrogen to L, is referred to herein as a "1,2,3,4-tetrahydroisoquinoline" for convenience in nomenclature, and this is the convention most commonly employed when naming compounds according to the invention as 2-substituted-1,2,3,4-tetrahydroisoquinolin-6-yl amides. It is noted that, less frequently when named as a substituent in a compound, this central ring system is also denoted as a 6-substituted "3,4-dihydro-1 H-isoquinolin-2-yl" moiety.

[0030] It will be appreciated by one of ordinary skill in the art that certain compounds of formula (I) contain an asymmetrically substituted carbon atom and accordingly may exist in, and be isolated in, both optically-active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the instant invention encompasses any racemic, optically-active, polymorphic, stereoisomeric, or mixture thereof, form of a formula (I) compound which form possesses properties useful in the methods and pharmaceutical compositions of this invention. It is well known, or will be apparent in light of the instant disclosure, to one of ordinary skill in the art how to prepare such optically-active forms (for example, by resolution of the racemic form by) recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis or by chromatographic techniques) and how to determine the efficacy of such forms in carrying out the objectives of the present invention by the standard protocols described in detail hereinbelow.

[0031] Furthermore, one of ordinary skill in the art will recognize that certain combinations of substituents or moieties listed in this invention define compounds that will be less stable under physiological conditions (e.g., those compounds containing aminate or acetal linkages). Accordingly, such compounds are less preferred.

[0032] The term "aliphatic hydrocarbylene radical" means a divalent, open-chain organic radical containing carbon and hydrogen only. The radical serves as a linking group, denoted hereinabove as Y. The radical may be straight chain or branched and/or saturated or unsaturated, containing up to three unsaturated bonds, either double, triple or a mixture of double and triple. The two valences may be on different carbon atoms or on the same carbon atom, and thus the term "alkylidene" is subsumed under this definition. The radical will typically be classified as a (C₁-C₂₀)alkylene radical, a (C₂-C₂₀)alkenylene radical or a (C₂-C₂₀)alkynylene radical. Typically, the radical will contain 1-10 carbon atoms, although longer chains are certainly feasible and within the scope of this invention.

[0033] Alkylene radicals include those saturated hydrocarbon groups having 1-20, preferably 1-10 carbon atoms, derived by removing two hydrogen atoms from a corresponding saturated acyclic hydrocarbon. Illustrative values having 1-10 carbon atoms include straight chain radicals having the formula (CH₂)_n wherein n is 1 to 10, such as methylene, dimethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene, nonamethylene and so forth. Also included are alkylidene radicals such as ethylidene, propylidene, butylidene and sec-butylidene. Also included are branched isomers such as 1,1-dimethyldimethylene, 1,1-dimethyltetramethylene, 2,2-dimethyltrimethylene and 3,3-dimethylpentamethylene.

[0034] Alkenylene radicals include those straight or branched chain radicals having 2-20 carbon atoms, preferably 2-10 carbon atoms, derived by removal of two hydrogen atoms from a corresponding acyclic hydrocarbon group containing at least one double bond. Illustrative values for alkenylene radicals having one double bond include ethenylene (vinylene), propenylene, 1-butenylene, 2-butenylene and isobutenylene. Alkenylene radicals containing two double bonds (sometimes referred to in the art as alkadienylene radicals) include 3-methyl-2,6-heptadienylene, 2-methyl-2,4-heptadienylene, 2,8-nonadienylene, 3-methyl-2,6-octadienylene and 2,6-decadienylene. An illustrative value for an alkylene radical containing three double bonds (an alkatrienylene radical) is 9,11,13-heptadecatrienylene.

[0035] Alkynylene radicals include those straight or branched chain radicals having 2-20 carbon atoms, preferably 2-10 carbon atoms, derived by removal of two hydrogen atoms from a corresponding acyclic hydrocarbon group containing at least one triple bond. Illustrative values include ethynylene, propynylene, 1-butyne, 1-pentyne, 1-hexynylene, 2-butyne, 2-pentyne, 3,3-dimethyl-1-butyne and so forth.

[0036] The following are illustrative values for other moieties and substituents named hereinabove, which are not to be construed as limiting in any respect. It is noted that throughout the description and appendant claims, if a cyclic or

polycyclic radical which can be bonded through differing ring atoms is referred to without noting a specific point of attachment, all possible points are intended, whether through a carbon atom or a trivalent nitrogen atom. As examples, reference to (unsubstituted) "naphthyl" means naphth-1-yl, and naphth-2-yl; reference to "pyridyl" means 2-, 3-, or 4-pyridyl and reference to "indolyl" means attachment or bonding through any of the 1-, 2-, 3-, 4-, 5-, 6- or 7-positions.

[0037] Illustrative values for (C₁-C₁₀)alkoxy include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, hexoxy, heptoxy and so forth.

[0038] Illustrative values for (C₁-C₁₀)alkylthio include the corresponding sulfurcontaining compounds of (C₁-C₁₀)alkoxy hereinabove including methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, pentylthio, hexylthio, heptylthio and so forth.

[0039] Illustrative values for (C₁-C₁₀)acyl include values for (C₁-C₁₀)alkanoyl such as formyl, acetyl, propionyl, butyryl and isobutyryl. Also included are other common cycle-containing radicals such as benzoyl.

[0040] Illustrative values for (C₁-C₁₀)acyloxy include values for (C₁-C₁₀)alkanoyloxy such as formyloxy, acetyloxy, propionyloxy, butyryloxy and isobutyryloxy. Also included are other cycle-containing radicals such as benzoyloxy.

[0041] Illustrative values for (C₁-C₁₀)alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl and isobutoxycarbonyl.

[0042] Illustrative values for (C₁-C₁₀)alkylamino include methylamino, ethylamino, propylamino, isopropylamino, butylamino and isobutylamino.

[0043] Illustrative values for di-(C₁-C₁₀)alkylamino include dimethylamino, diethylamino, dipropylamino, dibutylamino and diisobutylamino.

[0044] Illustrative values for (C₆-C₁₀)aryl(C₁-C₁₀)alkylamino are benzylamino, (1-phenylethyl)amino and (2-phenylethyl)amino.

[0045] Illustrative values for (C₆-C₁₀)aryl include phenyl and naphthyl.

[0046] Illustrative values of (C₃-C₈)cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0047] Illustrative values for fused benz derivatives of (C₃-C₈)cycloalkyl include 1,2,3,4-tetrahydronaphthalenyl, indanyl and fluorenyl.

[0048] Illustrative values of polycycloalkyl include adamantyl and 2-bicyclo[2.2.1]heptyl.

[0049] Illustrative values for (C₄-C₈)cycloalkenyl include cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl.

[0050] Illustrative values for polycycloalkenyl include bicyclo[3.1.1]hept-2-enyl.

[0051] Illustrative values for (C₆-C₁₀)aryloxy include phenoxy and naphthyloxy.

[0052] Illustrative values for (C₆-C₁₀)arylthio include phenylthio and naphthylthio.

[0053] Illustrative values for (C₆-C₁₀)aryl(C₁-C₁₀)alkoxy include benzyloxy and phenylethoxy.

[0054] Illustrative values for (C₆-C₁₀)aryl(C₁-C₁₀)alkylthio include benzylthio and phenylethylthio.

[0055] Illustrative values for (C₃-C₈)cycloalkyloxy include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy.

[0056] Illustrative values for (C₄-C₈)cycloalkenyloxy include cyclobutenyloxy, cyclopentenylloxy, cyclohexenyloxy and cycloheptenyloxy.

[0057] Illustrative values for heterocyclic substituents which are five-membered monocyclic radicals include furanyl, thienyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-thiadiazolyl and the like.

[0058] Illustrative values for heterocyclic substituents which are six-membered monocyclic radicals include 2H- and 4H-pyranyl, pyridyl, piperidinyl, piperazinyl, pyridazinyl, pyrimidinyl, pyrazinyl, morpholinyl, thiomorpholinyl, 1,3,5-triazinyl and the like.

[0059] Illustrative values for heterocyclic substituents which are fused benz derivatives of five-membered heterocyclic radicals include indolyl, isoindolyl, indolinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl and carbazolyl.

[0060] Illustrative values for heterocyclic substituents which are fused benz derivatives of six-membered heterocyclic radicals include quinolinyl, isoquinolinyl, quinazolinyl, phthalazinyl, phenothiazinyl, acridinyl and phenoxazinyl.

[0061] Illustrative examples for heterocyclic groups which are fused polycyclic radicals other than the fused benz systems exemplified hereinabove include purinyl and pteridinyl.

[0062] Illustrative values of (C₁-C₁₀)alkyl include methyl, ethyl, propyl, isopropyl, isobutyl, butyl, tert-butyl, pentyl, hexyl and the like.

[0063] Illustrative values for (C₁-C₃)perfluoroalkyl include trifluoromethyl, pentafluoroethyl and heptafluoropropyl.

[0064] Illustrative values for (C₁-C₃)perfluoroalkoxy include trifluoromethoxy, pentafluoroethoxy.

[0065] The compounds of formula (I), the stereoisomers and hydrates thereof, and the pharmaceutically acceptable salts of the compounds, stereoisomers and hydrates, are readily prepared according to the synthetic methodologies disclosed in the aforementioned PCT International Application Nos. WO 96/40640 and WO 98/23593.

[0066] The compound BMS-197636, also known as 9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-

N-propyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof, may be prepared as disclosed in PCT International Application Publication No. WO 96/26205, the disclosure of which is incorporated herein by reference.

[0067] The compound BMS-200150, also known as 2-[1-(3,3-diphenylpropyl)-4-piperidiny]-2,3-dihydro-1H-isoindol-1-one, and the pharmaceutically acceptable salts thereof, may be prepared as disclosed in European Patent Application No. EP 0 643 057, the disclosure of which is also incorporated herein by reference.

[0068] The compound BMS-201038, also known as 9-[4-(4-[2-(4-trifluoromethylphenyl)benzoylamino]piperidin-1-yl)butyl]-N-2,2,2-trifluoroethyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof, may be prepared as disclosed in U.S. Pat. No. 5,739,135, the disclosure of which is also incorporated herein by reference.

[0069] Although any anti-obesity agent may be employed in the methods and pharmaceutical compositions of the instant invention, generally preferred anti-obesity agents are selected from the group consisting of a β_3 -adrenergic receptor agonist, a cholecystokinin-A (CCK-A) agonist, a monoamine reuptake inhibitor (such as sibutramine), a sympathomimetic agent, a serotonergic agent (such as dexfenfluramine or fenfluramine), a dopamine agonist (such as bromocriptine), a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone receptor analog, a cannabinoid receptor antagonist, a melanin concentrating hormone antagonist, the OB protein (hereinafter referred to as leptin), a leptin analog, a leptin receptor agonist, a galanin antagonist, or a lipase inhibitor (such as orlistat). Other anti-obesity agents may include anorectic agents, for example, a bombesin agonist, a Neuropeptide-Y antagonist, a thyromimetic agent, dehydroepiandrosterone or an analog thereof, a glucocorticoid receptor agonist or antagonist, an orexin receptor antagonist, a urocortin binding protein antagonist, a glucagon-like peptide-1 receptor agonist, a ciliary neurotrophic factor, such as Axokine, or a human agouti-related protein (hereinafter referred to as AGRP) antagonist. Other anti-obesity agents useful in the practice of the instant invention are known, or will be apparent in light of this disclosure, to one of ordinary skill in the art.

[0070] Particularly preferred anti-obesity agents useful in the methods of the invention comprise β_3 -adrenergic receptor agonists, sibutramine, orlistat, fenfluramine, dexfenfluramine, bromocriptine, phentermine, ephedrine, leptin, phenylpropanolamine, and pseudoephedrine.

[0071] Particularly preferred β_3 -adrenergic receptor agonists include those substituted aminopyridines disclosed in commonly assigned PCT International Application Publication No. WO 96/35671, the disclosure of which is incorporated herein by reference. Especially preferred β_3 -adrenergic receptor agonists disclosed therein are selected from the group consisting of {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenyl}acetic acid, {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenyl}benzoic acid, {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenyl}propionic acid, and {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenoxy}acetic acid.

[0072] The particularly preferred anorectic agent phentermine may be prepared as described in U.S. Patent No. 2,408,345, the disclosure of which is incorporated herein by reference.

[0073] The particularly preferred monoamine reuptake inhibitor sibutramine may be prepared as described in U.S. Patent No. 4,929,629, the disclosure of which is incorporated herein by reference.

[0074] The particularly preferred lipase inhibitor orlistat may be prepared as described in U.S. Patent No. 4,598,089, the disclosure of which is incorporated herein by reference.

[0075] The particularly preferred serotonergic agents fenfluramine and dexfenfluramine may be prepared as described in U.S. Patent No. 3,198,834, the disclosure of which is incorporated herein by reference.

[0076] The particularly preferred dopamine agonist bromocriptine may be prepared as described in U.S. Patent Nos. 3,752,814 and 3,752,888, the disclosures of which are incorporated herein by reference.

[0077] The dosage of the apo B secretion/MTP inhibitor administered will generally be dependent upon the health of the subject being treated, the extent of decreased intestinal fat absorption desired, the nature and kind of concurrent therapy, if any, and the frequency of treatment and nature of the effect desired. In general, apo B secretion/MTP inhibitors have been reported with representative dosage ranges being from about 0.01 mg/kg/day to about 15.0 mg/kg/day. Generally preferable dosages range from about 0.1 mg/kg/day to about 1.0 mg/kg/day. However, some variability in the general dosage range may be required depending upon the age, weight, and species of the patient, the intended route of administration, and the degree of intestinal fat absorption reduction desired.

[0078] The dosage of the anti-obesity agent is generally in the range of from about 0.001 to about 50 mg/kg body weight of the subject per day, preferably from about 0.1 to about 10 mg/kg body weight of the subject per day, administered as a single or divided dose.

[0079] When the anti-obesity agent is phentermine, the dosage of phentermine is from about 0.01 to about 10 mg/kg body weight of the subject per day, preferably from about 0.1 to about 1 mg/kg body weight of the subject per day.

[0080] When the anti-obesity agent is sibutramine, the dosage of sibutramine is from about 0.01 to about 30 mg/kg body weight of the subject per day, preferably from about 0.1 to about 1 mg/kg body weight of the subject per day.

[0081] When the anti-obesity agent is fenfluramine or dexfenfluramine, the dosage range of fenfluramine or dexfenfluramine is from about 0.01 to about 30 mg/kg body weight of the subject per day, preferably from about 0.1 to about

1 mg/kg body weight of the subject per day.

[0082] When the anti-obesity agent is bromocriptine, the dosage range of bromocriptine is from about 0.01 to about 10 mg/kg body weight of the subject per day, preferably from about 0.1 to about 10 mg/kg body weight of the subject per day.

[0083] According to the methods of the invention, when the apo B secretion/MTP inhibitors, the hydrates and stereoisomers thereof, and the pharmaceutically acceptable salts of the compounds, hydrates and stereoisomers, and the anti-obesity agents are administered together, such administration can be sequential in time or simultaneous with the simultaneous method being generally preferred. For sequential administration, the apo B secretion/MTP inhibitor, a hydrate or stereoisomer thereof, or a pharmaceutically acceptable salt of the inhibitor, hydrate or stereoisomer, and the anti-obesity agent can be administered in any order. It is generally preferred that such administration be oral. It is especially preferred that the administration be oral and simultaneous. However, if the subject being treated is unable to swallow, or oral absorption is otherwise impaired or undesirable, parenteral or transdermal administration will be appropriate. When the apo B secretion/MTP inhibitor, a hydrate or stereoisomer thereof, or a pharmaceutically acceptable salt of the inhibitor, hydrate or stereoisomer, and the anti-obesity agent are administered sequentially, the administration of each can be by the same method or by different methods.

[0084] According to the methods of the invention, an apo B secretion/MTP inhibitor, a hydrate or stereoisomer thereof, or a pharmaceutically acceptable salt of the inhibitor, hydrate or stereoisomer, employed alone or with an anti-obesity agent, is preferably administered in the form of a pharmaceutical composition comprising a pharmaceutically acceptable carrier, vehicle or diluent. Accordingly, an apo B secretion/MTP inhibitor, a hydrate or stereoisomer thereof, or a pharmaceutically acceptable salt of the inhibitor, hydrate or stereoisomer of this invention, can be administered alone or with an anti-obesity agent, in any conventional oral, parenteral or transdermal dosage form.

[0085] Suitable pharmaceutically-acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. According to the methods of the invention, the apo B secretion/MTP inhibitor, a hydrate or stereoisomer thereof, or a pharmaceutically acceptable salt of the inhibitor, hydrate or stereoisomer, employed alone or with an anti-obesity agent, will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the ranges described hereinabove. Thus, for oral administration, the compounds can be combined with a suitable solid or liquid carrier, vehicle or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions may, if desired, contain additional components such as flavorants, sweeteners, excipients and the like.

[0086] The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

[0087] Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

[0088] The pharmaceutical compositions of the invention may also be administered parenterally. For parenteral administration the pharmaceutical compositions can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. Solutions or suspensions of these pharmaceutical compositions can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in sesame or peanut oil, ethanol, water, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, vegetable oils, N-methyl glucamine, polyvinylpyrrolidone and mixtures thereof in oils as well as aqueous solutions of water-soluble pharmaceutically acceptable salts of the compounds. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being the preferred parenteral route in humans. Solutions prepared for intravenous administration are preferably rendered isotonic prior to usage.

[0089] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and preserved against contamination by microorganisms including bacteria and fungi.

[0090] The pharmaceutical compositions may also be administered transdermally. Suitable formulations for transdermal application include an effective intestinal fat absorption reducing amount of an apo B secretion/MTP inhibitor, a hydrate or stereoisomer thereof, or a pharmaceutically acceptable salt of the inhibitor, hydrate or stereoisomer, employed alone or with an anti-obesity agent, or a pharmaceutical composition thereof, with a suitable transdermal carrier. Preferred transdermal carriers include absorbable pharmacologically acceptable solvents to promote and assist pas-

sage through the skin of the subject being treated. Characteristically, transdermal devices comprise the form of a bandage having a backing member, a reservoir containing the compound, optionally with carriers, optionally a rate-controlling barrier to deliver the compound to the skin of the subject being treated at a controlled and predetermined rate over a prolonged period of time and means to secure the device to the skin of the subject being treated.

[0091] Methods of preparing the various pharmaceutical compositions with a desired amount of an active ingredient are known, or will be apparent in light of this disclosure, to one of ordinary skill in the art. See, for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, 18th Edition (1990).

[0092] As a consequence of their ability to reduce intestinal fat absorption, the methods and pharmaceutical compositions of the instant invention also have utility in reducing the absorption of intestinal fat in companion animals, preferably dogs and cats, and livestock, such as cows, pigs, and the like. The administration of the pharmaceutical compositions according to the methods of the invention may be effected orally, parenterally or transdermally. An amount of a pharmaceutical composition of the invention is administered such that an effective dose is received, normally a daily dose, as set forth hereinabove.

[0093] Conveniently, the medicaments can be carried in the drinking water such that a therapeutic dosage of the agents is ingested with the daily water supply. The agents can be directly metered into drinking water, preferably in the form of a liquid, water-soluble concentrate, such as an aqueous solution of a water-soluble salt.

[0094] For purposes of alternative convenience, the active ingredients can also be added directly to the companion animal's feed, as such, or in the form of an animal feed supplement, also referred to as a premix or concentrate. A premix or concentrate of the therapeutic agent in a carrier is more commonly employed for the inclusion of the agent in the feed. Suitable carriers are liquid or solid, as desired, such as water, various meals such as alfalfa meal, soybean meal, cottonseed oil meal, linseed oil meal, corncob meal and corn meal, molasses, urea, bone meal, and various mineral mixes. A particularly effective carrier is the respective animal feed itself, i.e., a small portion of such feed. The carrier facilitates uniform distribution of the active materials in the finished feed with which the premix is blended. It is important that the compounds be thoroughly blended into the premix and, subsequently, the feed. In this respect, the agents may be dispersed or dissolved in a suitable oily vehicle such as soybean oil, corn oil, cottonseed oil, and the like, or in a volatile organic solvent and then blended with the carrier. It will be appreciated that the proportions of active materials in the concentrate are capable of wide variation since the amount of agent in the finished feed may be adjusted by blending the appropriate proportion of premix with the feed to obtain a desired level of the therapeutic agents.

[0095] High potency concentrates may be blended by the feed manufacturer with a proteinaceous carrier such as soybean oil meal and other meals, as described above,) to produce concentrated supplements which are suitable for direct feeding to animals. In such instances, the animals are permitted to consume the usual diet. Alternatively, such concentrated supplements may be added directly to the feed to produce a nutritionally balanced, finished feed containing a therapeutically effective level of a compound according to this invention. The mixtures are thoroughly blended by standard procedures, such as in a twin shell blender, to insure homogeneity. If the supplement is used as a top dressing for the feed, it likewise helps to insure uniformity of distribution of the active ingredient across the top of the dressed feed.

[0096] For veterinary uses, both paste and pellet formulations may also be conveniently employed. Paste formulations can be prepared readily by dispersing the active compounds in a pharmaceutically acceptable oil such as peanut oil, sesame oil, corn oil, and the like. Similarly, pellets containing an effective amount of the compounds of the instant invention can be prepared by admixing the compounds of this invention with a suitable diluent such as carbowax, camuba wax, and the like, and a lubricant, such as magnesium or calcium stearate, can be employed to improve the pelleting process.

[0097] Since the instant invention relates to the reduction of intestinal fat absorption with a combination of active ingredients which may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. A kit, according to this invention, comprises two separate pharmaceutical compositions: a first unit dosage form comprising an apo B secretion/MTP inhibitor, preferably a compound selected from the group consisting of: (i) a compound of formula (I), a stereoisomer or hydrate thereof, or a pharmaceutically acceptable salt of said compound, stereoisomer or hydrate; (ii) the compound 9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof; (iii) the compound 2-[1-(3,3-diphenylpropyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one, and the pharmaceutically acceptable salts thereof; and (iv) the compound 9-[4-(4-[2-(4-trifluoromethylphenyl)benzoylamino]piperidin-1-yl)butyl]-N-2,2,2-trifluoroethyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof; and a pharmaceutically acceptable carrier, vehicle or diluent; a second unit dosage form comprising an anti-obesity agent, and a pharmaceutically acceptable carrier, vehicle or diluent; and a container. The container is used to contain the separate pharmaceutical compositions and may comprise, for example, a divided bottle or a divided foil packet, however, the separate pharmaceutical compositions may also be contained within a single, undivided container. Normally, the kit will also include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered

at different dosage levels, or when titration of the individual components of the combination is desired by the prescribing physician.

[0098] One example of such a kit comprises a so-called blister pack. Blister packs are well known in the packaging industry and are being used widely for the packaging of pharmaceutical unit dosage forms (tablets, capsules and the like). Blister packs generally comprise a sheet of relatively rigid material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses generally conform to the size and shape of the tablets or capsules to be contained therein. Next, the tablets or capsules are placed in the recesses and the sheet of relatively rigid material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably, the strength of the sheet is such that the tablets or capsules may be removed from the blister pack by the application of manual pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed through the formed opening.

[0099] It is further desirable to provide a memory aid on the pack e.g., in the form of numbers or similar indicia next to the tablets or capsules whereby the indicia correspond with the days of the regimen which the dosage form so specified is to be ingested. An additional example of such a memory aid is a calendar printed on the pack, e.g., as follows "First Week, Monday, Tuesday, ... etc.... Second Week, Monday, Tuesday,... " etc. Other variations will be readily apparent. A "daily dose" can be a single tablet or capsule or multiple tablets or capsules to be ingested on a given day. Also, a daily dose comprising an apo B secretion/MTP inhibitor, preferably a compound selected from the group consisting of: (i) a compound of formula (I), a stereoisomer or hydrate thereof, or a pharmaceutically acceptable salt of said compound, stereoisomer or hydrate; (ii) the compound 9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof; (iii) the compound 2-[1-(3,3-diphenylpropyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one, and the pharmaceutically acceptable salts thereof; and (iv) the compound 9-[4-(4-[2-(4-trifluoromethylphenyl)benzoylamino]piperidin-1-yl)butyl]-N-2,2,2-trifluoroethyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof; can consist of one tablet or capsule, while a daily dose comprising an anti-obesity agent can consist of multiple tablets or capsules, or vice versa. The memory aid should reflect this.

[0100] In another specific embodiment of the invention, a pack designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the pack is equipped with a memory aid, so as to further facilitate compliance with the dosage regimen. An example of such a memory aid is a mechanical counter which indicates the number of daily doses to be dispensed. Another example of such a memory aid is a battery-powered microchip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds the patient when the next dose is to be taken.

EXPERIMENTAL

[0101] The utility of the apo B secretion/MTP inhibitors 4'-trifluoromethyl-biphenyl-2-carboxylic acid-[2-(2-acetylaminooethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl] amide and 4'-trifluoromethyl-biphenyl-2-carboxylic acid-(2-butyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide in the reduction of intestinal fat absorption according to the practice of the methods of the invention was demonstrated according to the following protocol.

[0102] Healthy, young adult (1-2 years of age) male beagles (Marshall Farms, North Rose, New York, NY 14516) weighing 11.45 - 12.45 kg at the start of the treatment period were employed as test subjects. The animals were housed individually in standard caging meeting or exceeding the USDA regulations (U.S. Department of Agriculture, Animal Welfare, Final Rules. 9 C.F.R. Parts 1-3, 1995).

[0103] The test compound was provided as a water-soluble powder. The dosing solution, administered by oral gavage, was provided employing a 0.025 M citrate buffer (approx. pH = 3) prepared using anhydrous citric acid (0.4 g/mL) and anhydrous sodium citrate (0.1 g/mL) as the test vehicle. The dosing solution was prepared at 0.5 mg/mL activity so that 1 mL was delivered per kg body weight. Following a fourteen day acclimation period (designated as Days -14 to -1), during which time the test animals were evaluated for certain criteria including determination of body weight, physical examinations, and initial fecal specimen collection, a sixteen day evaluation study was effected.

[0104] The study consisted of one group of animals containing five dogs. On Days 0 and 5-12, each dog received the dosing solution administered as a single dose at Time 0 on each dosing day via a feeding tube. This was followed by a 10 mL water rinse to ensure total delivery of dosing solution. Each test animal was permitted *ad libitum* access to water and Pedigree Mealttime® (Kal Kan Pet Care; Vernon, CA) dry food each day during the study.

[0105] Fecal specimens were collected daily over approximately 24 hours (± 1 hr) prestudy and then beginning on Day -2 and terminating on Day 16. The fecal specimens so collected were weighed (total grams of bulk feces) frozen, stored at -26°C to -20°C and then analyzed for fecal fat content.

[0106] An adaptation of the method of Freidner, et al., Clin. Chem. Acta, 18, 345-349 (1967) was employed for the gravimetric determination of fecal fat content. Modifications of the original procedure were as follows: (1) the 5 g fecal

fat sample was weighed into a tared 50 mL centrifuge tube, rather than weighing the tube before and after the sample was added, and (2) for shaking, the tubes were placed horizontally on a flatbed shaker rather than being placed upright in a paint can on a paint shaker.

[0107] The required number of crystallizing dishes (three per sample) were weighed (to 0.0001 g accuracy). Each fecal sample was thawed overnight at room temperature and then thoroughly mixed to homogeneity by manipulation through the plastic bag. The sample was then flattened in the bag to approximately 1 cm thickness and divided into rectangles about 2 cm x 3 cm. Three aliquots (approximately 5 g each) were taken from various sections of the total sample and each was transferred to a tared 50 mL centrifuge tube. Each aliquot was weighed (sample weights to 0.01 accuracy), then approximately 10 g of glass beads and 10mL of 0.4% amyl alcohol in absolute ethanol were added to each tube, and the tubes were shaken horizontally for 12 minutes at high speed on a flatbed shaker. The samples were acidified with 3mL of 2N HCl, and 30 mL of petroleum ether was added. The tubes were shaken as above for 2 minutes and then centrifuged at 1,000 rpm for 5 minutes to separate the phases. A 25 mL aliquot of the petroleum ether layer from each tube was transferred to a pre-weighed crystallizing dish. An additional 25 mL of petroleum ether was added to each tube and the tubes were shaken 1-2 minutes and centrifuged as above. Once more, 25 mL of the petroleum ether layer was transferred to the appropriate crystallizing dish. This step was repeated. The crystallizing dishes were covered with tissue paper and left overnight in a fume hood to allow for evaporation. The following morning, the crystallizing dishes + dry residue were weighed to 0.0001 g accuracy.

[0108] The calculations of fecal fat were carried out as follows:

sample wt. = S

residue wt. (R) = (crystallizing dish + residue) - (empty crystallizing dish)

fecal fat (F) = R/S (units are grams fat/gram wet weight)

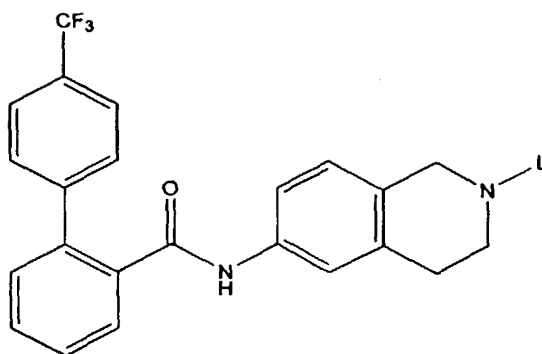
total fat = F x total grams of bulk feces

[0109] In the intestinal fat absorption reduction determination protocol described hereinabove, the test compounds 4'-trifluoromethyl-biphenyl-2-carboxylic acid-[2-(2-acetyl aminoethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl] amide and 4'-trifluoromethyl-biphenyl-2-carboxylic acid-(2-butyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide reduced intestinal fat absorption in dogs by 49% and 26% respectively.

Claims

1. A method of reducing intestinal fat absorption in an animal which comprises administering to an animal in need of such reduction an intestinal fat absorption reducing amount of an apolipoprotein B secretion/microsomal triglyceride transfer protein inhibitor.
2. A method according to claim 1 wherein said apolipoprotein B secretion/microsomal triglyceride transfer protein inhibitor is a compound selected from the group consisting of:

(i) a compound of formula (I)



(I)

the stereoisomers and hydrates thereof, and the pharmaceutically acceptable salts of said compounds, stereoisomers and hydrates, wherein L represents:

X-Y-Z, wherein:

X is a moiety selected from the group consisting of CH₂, CO, CS, or SO₂;

Y is a moiety selected from the group consisting of a direct link, aliphatic hydrocarbylene radicals having up to 20 carbon atoms, which radical may be monosubstituted by hydroxy, (C₁-C₁₀)alkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)acyloxy, or (C₆-C₁₀)aryl, NH, and O, provided that if X is CH₂, Y is a direct link; and

Z is a moiety selected from the group consisting of:

- (1) hydrogen, halogen, cyano,
- (2) hydroxy, (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkylthio, (C₁-C₁₀)acyl, thiophenylcarbonyl, (C₁-C₁₀)alkoxycarbonyl,
- (3) (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₆-C₁₀)aryl(C₁-C₁₀)alkylamino, provided that Y is not O or NH,
- (4) unsubstituted vinyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl and fused benz derivatives thereof, (C₇-C₁₀)polycycloalkyl, (C₄-C₈)cycloalkenyl, (C₇-C₁₀)polycycloalkenyl,
- (5) (C₆-C₁₀)aryloxy, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryl(C₁-C₁₀)alkoxy, (C₆-C₁₀)aryl(C₁-C₁₀)alkylthio, (C₃-C₈)cycloalkyloxy, (C₄-C₈)cycloalkenyloxy,
- (6) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5 to 14 ring atoms, wherein said radicals contain a total of from 1 to 4 ring heteroatoms independently selected from oxygen, nitrogen, and sulfur, and wherein the individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, provided that if X is CH₂, Z is H or is selected from groups (4) and (6),

wherein, when Z contains one or more rings, said rings may each independently bear 0 to 4 substituents independently selected from halo, hydroxy, cyano, nitro, oxo, thio, aminosulfonyl, phenyl, phenoxy, phenylthio, halophenylthio, benzyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylamino(C₁-C₁₀)alkoxy, (C₁-C₃)perfluoroalkyl, (C₁-C₃)perfluoroalkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)acyloxy, (C₁-C₁₀)acyloxy(C₁-C₁₀)alkyl, and pyrrolidinyl; or

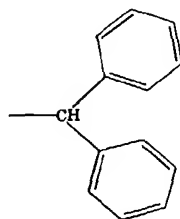
G, wherein G is selected from the group consisting of:

- (a) a phenyl or heterocyclic ring wherein said heterocyclic ring contains a total of from 3 to 14 ring atoms, wherein said heterocyclic ring incorporates a total of from 1 to 4 ring heteroatoms selected independently from oxygen, nitrogen, and sulfur, wherein the individual rings of said heterocyclic ring may be independently saturated, partially saturated or aromatic, and wherein each of said phenyl or heterocyclic rings may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thio, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, ben-

zyloxy, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acyloxy, (C₁-C₆)acylamino and (C₁-C₆)perfluoroacylamino;

(b)-CH₂CN,

(c)



(d) (C₂-C₁₂)alkyl or (C₂-C₁₂)perfluoroalkyl wherein each of said (C₂-C₁₂)alkyl and (C₂-C₁₂)perfluoroalkyl is substituted optionally with from 1-3 substituents selected independently from:

(1) phenyl, halogen, nitro, cyano, hydroxy, -NR¹R², -OCOR³, (C₁-C₄)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)thioalkoxy or (C₁-C₄)perfluorothioalkoxy,

where R¹ and R² in the definition of -NR¹R² are each selected independently from hydrogen, formyl, phenyl, benzyl, benzoyl, (C₃-C₈)cycloalkyl, (C₃-C₈)cycloalkenyl, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₆)acyl, (C₁-C₆)perfluoroacyl, aminocarbonyl, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, aminosulfonyl, (C₁-C₄)alkylaminosulfonyl, di(C₁-C₄)alkylaminosulfonyl, (C₁-C₄)perfluoroalkylaminosulfonyl, di(C₁-C₄)perfluoroalkylaminosulfonyl, (C₁-C₄)alkylsulfonyl, and (C₁-C₄)perfluoroalkylsulfonyl,

or where R¹ and R², taken together with the nitrogen atom to which they are attached, form a saturated, partially-saturated or aromatic heterocyclic ring, wherein said heterocyclic ring contains a total of from 3 to 14 ring atoms and incorporates optionally an additional 1 to 4 ring heteroatoms selected independently from oxygen, nitrogen and sulfur, wherein said heterocyclic ring may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acylamino, and (C₁-C₁₀)acyloxy,

where R³ in the definition of -OCOR³ is selected from -NR¹R², phenyl, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₆)alkoxy and (C₁-C₆)perfluoroalkoxy,

(2) (C₃-C₈)cycloalkyl or (C₃-C₈)cycloalkenyl wherein each of said (C₃-C₈)cycloalkyl and (C₃-C₈)cycloalkenyl may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acylamino, (C₁-C₁₀)perfluoroacylamino, (C₁-C₁₀)acyloxy, and

(3) a saturated, partially-saturated or aromatic heterocyclic ring containing a total of from 3 to 14 ring atoms, wherein said heterocyclic ring incorporates a total of from 1 to 4 ring heteroatoms selected independently from oxygen, nitrogen and sulfur, wherein said heterocyclic ring may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acylamino, (C₁-C₁₀)perfluoroacylamino, (C₁-C₁₀)acyloxy;

(e) (C₃-C₈)cycloalkyl or (C₃-C₈)cycloalkenyl wherein each of said (C₃-C₈)cycloalkyl and (C₃-C₈)cy-

cloalkenyl may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acylamino, (C₁-C₁₀)perfluoroacylamino, (C₁-C₁₀)acyloxy; and

(f) $-(CH_2)_nCOR^4$, where R⁴ in the definition of $-(CH_2)_nCOR^4$ is selected from hydroxy, phenyl, -NR¹R², (C₁-C₄), (C₁-C₄)perfluoroalkyl, (C₁-C₄)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₃-C₈)cycloalkyl, and (C₃-C₈)cycloalkenyl, where n is an integer from 1 to 4;

(ii) the compound 9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof;

(iii) the compound 2-[1-(3,3-diphenylpropyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one, and the pharmaceutically acceptable salts thereof; and

(iv) the compound 9-[4-(4-[2-(4-trifluoromethylphenyl)benzoylamino]piperidin-1-yl)butyl]-N-2,2,2-trifluoroethyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof.

3. A method according to claim 2 wherein said apo B secretion/microsomal triglyceride transfer protein inhibitor is a compound selected from the group consisting of:

4'-trifluoromethyl-biphenyl-2-carboxylic acid-(2-butyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide, the hydrates thereof, and the pharmaceutically acceptable salts of said compound and said hydrates;

4'-trifluoromethyl-biphenyl-2-carboxylic acid-[2-(2-acetylaminoethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl] amide, the hydrates thereof, and the pharmaceutically acceptable salts of said compound and said hydrates;

9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof;

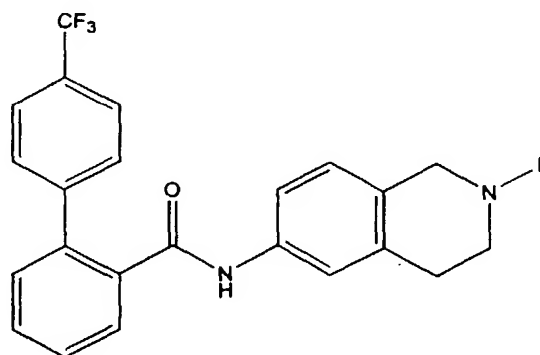
2-[1-(3,3-diphenylpropyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one, and the pharmaceutically acceptable salts thereof; and

9-[4-(4-[2-(4-trifluoromethylphenyl)benzoylamino]piperidin-1-yl)butyl]-N-2,2,2-trifluoroethyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof.

4. A method of reducing intestinal fat absorption in an animal which comprises administering to an animal in need of such reduction an intestinal fat absorption reducing amount of an apolipoprotein B secretion/microsomal triglyceride transfer protein inhibitor, and an amount of anti-obesity agent.

5. A method according to claim 4, wherein said apolipoprotein B secretion/microsomal triglyceride transfer protein inhibitor is a compound selected from the group consisting of:

(i) a compound of formula (I)



(I)

the stereoisomers and hydrates thereof, and the pharmaceutically acceptable salts of said compounds, stereoisomers and hydrates, wherein L represents:

X-Y-Z, wherein:

X is a moiety selected from the group consisting of CH₂, CO, CS, or SO₂ ;

Y is a moiety selected from the group consisting of a direct link, aliphatic hydrocarbylene radicals having up to 20 carbon atoms, which radical may be monosubstituted by hydroxy, (C₁-C₁₀)alkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)acyloxy, or (C₆-C₁₀)aryl, NH, and O, provided that if X is CH₂, Y is a direct link; and

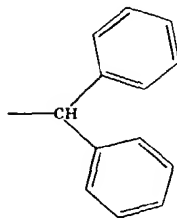
Z is a moiety selected from the group consisting of:

- (1) hydrogen, halogen, cyano,
- (2) hydroxy, (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkylthio, (C₁-C₁₀)acyl, thiophenylcarbonyl, (C₁-C₁₀)alkoxycarbonyl,
- (3) (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₆-C₁₀)aryl(C₁-C₁₀)alkylamino, provided that Y is not O or NH,
- (4) unsubstituted vinyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl and fused benz derivatives thereof, (C₇-C₁₀)polycycloalkyl, (C₄-C₈)cycloalkenyl, (C₇-C₁₀)polycycloalkenyl,
- (5) (C₆-C₁₀)aryloxy, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryl(C₁-C₁₀)alkoxy, (C₆-C₁₀)aryl(C₁-C₁₀)alkylthio, (C₃-C₈)cycloalkyloxy, (C₄-C₈)cycloalkenyloxy,
- (6) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5 to 14 ring atoms, wherein said radicals contain a total of from 1 to 4 ring heteroatoms independently selected from oxygen, nitrogen, and sulfur, and wherein the individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, provided that if X is CH₂, Z is H or is selected from groups (4) and (6),

wherein, when Z contains one or more rings, said rings may each independently bear 0 to 4 substituents independently selected from halo, hydroxy, cyano, nitro, oxo, thio, aminosulfonyl, phenyl, phenoxy, phenylthio, halophenylthio, benzyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylamino(C₁-C₁₀)alkoxy, (C₁-C₃)perfluoroalkyl, (C₁-C₃)perfluoroalkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)acyloxy, (C₁-C₁₀)acyloxy(C₁-C₁₀)alkyl, and pyrrolidinyl; or

G, wherein G is selected from the group consisting of:

- (a) a phenyl or heterocyclic ring wherein said heterocyclic ring contains a total of from 3 to 14 ring atoms, wherein said heterocyclic ring incorporates a total of from 1 to 4 ring heteroatoms selected independently from oxygen, nitrogen, and sulfur, wherein the individual rings of said heterocyclic ring may be independently saturated, partially saturated or aromatic, and wherein each of said phenyl or heterocyclic rings may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thio, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acyloxy, (C₁-C₆)acylamino and (C₁-C₆)perfluoroacylamino;
- (b) -CH₂CN,
- (c)



- (d) (C₂-C₁₂)alkyl or (C₂-C₁₂)perfluoroalkyl wherein each of said (C₂-C₁₂)alkyl and (C₂-C₁₂)perfluoro-

alkyl is substituted optionally with from 1-3 substituents selected independently from:

(1) phenyl, halogen, nitro, cyano, hydroxy, $-NR^1R^2$, $-OCOR^3$, (C_1-C_4) alkoxy, (C_1-C_4) perfluoroalkoxy, (C_1-C_4) thioalkoxy or (C_1-C_4) perfluorothioalkoxy,

where R^1 and R^2 in the definition of $-NR^1R^2$ are each selected independently from hydrogen, formyl, phenyl, benzyl, benzoyl, (C_3-C_8) cycloalkyl, (C_3-C_8) cycloalkenyl, (C_1-C_4) alkyl, (C_1-C_4) perfluoroalkyl, (C_1-C_{10}) alkoxycarbonyl, (C_1-C_6) acyl, (C_1-C_6) perfluoroacyl, aminocarbonyl, (C_1-C_{10}) alkylaminocarbonyl, di (C_1-C_{10}) alkylaminocarbonyl, aminosulfonyl, (C_1-C_4) alkylaminosulfonyl, di (C_1-C_4) alkylaminosulfonyl, (C_1-C_4) perfluoroalkylaminosulfonyl, di (C_1-C_4) perfluoroalkylaminosulfonyl, (C_1-C_4) alkylsulfonyl, and (C_1-C_4) perfluoroalkylsulfonyl,

or where R^1 and R^2 , taken together with the nitrogen atom to which they are attached, form a saturated, partially-saturated or aromatic heterocyclic ring, wherein said heterocyclic ring contains a total of from 3 to 14 ring atoms and incorporates optionally an additional 1 to 4 ring heteroatoms selected independently from oxygen, nitrogen and sulfur, wherein said heterocyclic ring may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C_1-C_{10}) alkyl, (C_1-C_4) perfluoroalkyl, (C_1-C_{10}) alkoxy, (C_1-C_4) perfluoroalkoxy, (C_1-C_{10}) alkoxycarbonyl, (C_1-C_{10}) alkylthio, (C_1-C_{10}) alkylamino, di (C_1-C_{10}) alkylamino, (C_1-C_{10}) alkylaminocarbonyl, di (C_1-C_{10}) alkylaminocarbonyl, (C_1-C_{10}) acyl, (C_1-C_{10}) perfluoroacyl, (C_1-C_{10}) acylamino, and (C_1-C_{10}) acyloxy,

where R^3 in the definition of $-OCOR^3$ is selected from $-NR^1R^2$, phenyl, (C_1-C_{10}) alkyl, (C_1-C_4) perfluoroalkyl, (C_1-C_6) alkoxy and (C_1-C_6) perfluoroalkoxy,

(2) (C_3-C_8) cycloalkyl or (C_3-C_8) cycloalkenyl wherein each of said (C_3-C_8) cycloalkyl and (C_3-C_8) cycloalkenyl may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C_1-C_{10}) alkyl, (C_1-C_4) perfluoroalkyl, (C_1-C_{10}) alkoxy, (C_1-C_4) perfluoroalkoxy, (C_1-C_{10}) alkoxycarbonyl, (C_1-C_{10}) alkylthio, (C_1-C_{10}) alkylamino, di (C_1-C_{10}) alkylamino, (C_1-C_{10}) alkylaminocarbonyl, di (C_1-C_{10}) alkylaminocarbonyl, (C_1-C_{10}) acyl, (C_1-C_{10}) perfluoroacyl, (C_1-C_{10}) acylamino, (C_1-C_{10}) perfluoroacylamino, (C_1-C_{10}) acyloxy, and

(3) a saturated, partially-saturated or aromatic heterocyclic ring containing a total of from 3 to 14 ring atoms, wherein said heterocyclic ring incorporates a total of from 1 to 4 ring heteroatoms selected independently from oxygen, nitrogen and sulfur, wherein said heterocyclic ring may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C_1-C_{10}) alkyl, (C_1-C_4) perfluoroalkyl, (C_1-C_{10}) alkoxy, (C_1-C_4) perfluoroalkoxy, (C_1-C_{10}) alkoxycarbonyl, (C_1-C_{10}) alkylthio, (C_1-C_{10}) alkylamino, di (C_1-C_{10}) alkylamino, (C_1-C_{10}) alkylaminocarbonyl, di (C_1-C_{10}) alkylaminocarbonyl, (C_1-C_{10}) acyl, (C_1-C_{10}) perfluoroacyl, (C_1-C_{10}) acylamino, (C_1-C_{10}) perfluoroacylamino, (C_1-C_{10}) acyloxy;

(e) (C_3-C_8) cycloalkyl or (C_3-C_8) cycloalkenyl wherein each of said (C_3-C_8) cycloalkyl and (C_3-C_8) cycloalkenyl may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C_1-C_{10}) alkyl, (C_1-C_4) perfluoroalkyl, (C_1-C_{10}) alkoxy, (C_1-C_4) perfluoroalkoxy, (C_1-C_{10}) alkoxycarbonyl, (C_1-C_{10}) alkylthio, (C_1-C_{10}) alkylamino, di (C_1-C_{10}) alkylamino, (C_1-C_{10}) alkylaminocarbonyl, di (C_1-C_{10}) alkylaminocarbonyl, (C_1-C_{10}) acyl, (C_1-C_{10}) perfluoroacyl, (C_1-C_{10}) acylamino, (C_1-C_{10}) perfluoroacylamino, (C_1-C_{10}) acyloxy; and

(f) $-(CH_2)_nCOR^4$, where R^4 in the definition of $-(CH_2)_nCOR^4$ is selected from hydroxy, phenyl, $-NR^1R^2$, (C_1-C_4) alkyl, (C_1-C_4) perfluoroalkyl, (C_1-C_4) alkoxy, (C_1-C_4) perfluoroalkoxy, (C_3-C_8) cycloalkyl, and (C_3-C_8) cycloalkenyl, where n is an integer from 1 to 4;

(ii) the compound 9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof;

(iii) the compound 2-[1-(3,3-diphenylpropyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one, and the pharmaceutically acceptable salts thereof; and

(iv) the compound 9-[4-[4-[2-(4-trifluoromethylphenyl)benzoylamino]piperidin-1-yl]butyl]-N-2,2,2-trifluoroethyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof.

6. A method according to claim 5 wherein said apo B secretion/microsomal triglyceride transfer protein inhibitor is a

compound selected from the group consisting of:

4'-trifluoromethyl-biphenyl-2-carboxylic acid-(2-butyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide, the hydrates thereof, and the pharmaceutically acceptable salts of said compound and said hydrates;

4'-trifluoromethyl-biphenyl-2-carboxylic acid-[2-(2-acetylaminoethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl] amide, the hydrates thereof, and the pharmaceutically acceptable salts of said compound and said hydrates;

9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof;

2-[1-(3,3-diphenylpropyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one, and the pharmaceutically acceptable salts thereof; and

9-[4-(4-[2-(4-trifluoromethylphenyl)benzoylamino]piperidin-1-yl)butyl]-N-2,2,2-trifluoroethyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof

7. A method according to claim 4 wherein said anti-obesity agent is selected from the group consisting of a β_3 -adrenergic receptor agonist, a cholecystokinin-A agonist, a monoamine reuptake inhibitor, a sympathomimetic agent, a serotonergic agent, a dopamine agonist, a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone receptor analog, a cannabinoid receptor antagonist, a melanin concentrating hormone antagonist, leptin, a leptin analog, a leptin receptor agonist, a galanin antagonist, a lipase inhibitor, a bombesin agonist, a Neuropeptide-Y antagonist, a thyromimetic agent, dehydroepiandrosterone or an analog thereof, a glucocorticoid receptor agonist or antagonist, an orexin receptor antagonist, a urocortin binding protein antagonist, a glucagon-like peptide-1 receptor agonist, a ciliary neurotrophic factor, and a human agouti-related protein antagonist.

8. A method according to claim 7 wherein said anti-obesity agent is a compound selected from the group consisting of sibutramine, orlistat, fenfluramine, dexfenfluramine, bromocriptine, phentermine, ephedrine, leptin, phenylpropanolamine, pseudoephedrine, {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenyl}acetic acid, {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenyl}benzoic acid, {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenyl}propionic acid, and {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenoxy}acetic acid.

9. A method according to claim 4 wherein said apolipoprotein B secretion/microsomal triglyceride transfer protein inhibitor is a compound selected from the group consisting of:

4'-trifluoromethyl-biphenyl-2-carboxylic acid-(2-butyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide, the hydrates thereof, and the pharmaceutically acceptable salts of said compound and said hydrates;

4'-trifluoromethyl-biphenyl-2-carboxylic acid-[2-(2-acetylaminoethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl] amide, the hydrates thereof, and the pharmaceutically acceptable salts of said compound and said hydrates;

9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof;

2-[1-(3,3-diphenylpropyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one, and the pharmaceutically acceptable salts thereof; and

9-[4-(4-[2-(4-trifluoromethylphenyl)benzoylamino]piperidin-1-yl)butyl]-N-2,2,2-trifluoroethyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof; and

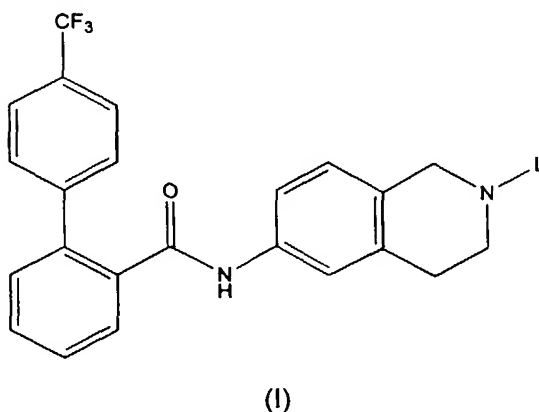
said anti-obesity agent is selected from the group consisting of a β_3 -adrenergic receptor agonist, a cholecystokinin-A agonist, a monoamine reuptake inhibitor, a sympathomimetic agent, a serotonergic agent, a dopamine agonist, a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone receptor analog, a cannabinoid receptor antagonist, a melanin concentrating hormone antagonist, leptin, a leptin analog, a leptin receptor agonist, a galanin antagonist, a lipase inhibitor, a bombesin agonist, a Neuropeptide-Y antagonist, a thyromimetic agent, dehydroepiandrosterone or an analog thereof, a glucocorticoid receptor agonist or antagonist, an orexin receptor antagonist, a urocortin binding protein antagonist, a glucagon-like peptide-1 receptor agonist, a ciliary neurotrophic factor, and a human agouti-related protein antagonist.

10. A method according to claim 9, wherein said anti-obesity agent is a compound selected from the group consisting of sibutramine, orlistat, fenfluramine, dexfenfluramine, bromocriptine, phentermine, ephedrine, leptin, phenylpropanolamine, pseudoephedrine, {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenyl}acetic acid, {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenyl}benzoic acid, {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenyl}propionic acid, and {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenoxy}acetic acid.

no)ethoxy]phenoxy}acetic acid.

11. A pharmaceutical composition comprising amounts of an apolipoprotein B secretion/microsomal triglyceride transfer protein inhibitor, and an anti-obesity agent.
12. A composition according to claim 11 further comprising a pharmaceutically acceptable carrier, vehicle or diluent.
13. A composition according to claim 11 wherein said apolipoprotein B secretion/microsomal triglyceride transfer protein inhibitor is a compound selected from the group consisting of:

(i) compound of formula (I)



the stereoisomers and hydrates thereof, and the pharmaceutically acceptable salts of said compounds, stereoisomers and hydrates, wherein L represents:

X-Y-Z, wherein:

X is a moiety selected from the group consisting of CH₂, CO, CS, or SO₂ ;

Y is a moiety selected from the group consisting of a direct link, aliphatic hydrocarbylene radicals having up to 20 carbon atoms, which radical may be monosubstituted by hydroxy, (C₁-C₁₀)alkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)acyloxy, or (C₆-C₁₀)aryl, NH, and O, provided that if X is CH₂, Y is a direct link; and

Z is a moiety selected from the group consisting of:

- (1) hydrogen, halogen, cyano,
- (2) hydroxy, (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkylthio, (C₁-C₁₀)acyl, thiophenylcarbonyl, (C₁-C₁₀)alkoxycarbonyl,
- (3) (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₆-C₁₀)aryl(C₁-C₁₀)alkylamino, provided that Y is not O or NH,
- (4) unsubstituted vinyl, (C₆-C₁₀)aryl, (C₃-C₈)cycloalkyl and fused benz derivatives thereof, (C₇-C₁₀)polycycloalkyl, (C₄-C₈)cycloalkenyl, (C₇-C₁₀)polycycloalkenyl,
- (5) (C₆-C₁₀)aryloxy, (C₆-C₁₀)arylthio, (C₆-C₁₀)aryl(C₁-C₁₀)alkoxy, (C₆-C₁₀)aryl(C₁-C₁₀)alkylthio, (C₃-C₈)cycloalkyloxy, (C₄-C₈)cycloalkenyloxy,
- (6) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5 to 14 ring atoms, wherein said radicals contain a total of from 1 to 4 ring heteroatoms independently selected from oxygen, nitrogen, and sulfur, and wherein the individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, provided that if X is CH₂, Z is H or is selected from groups (4) and (6),

wherein, when Z contains one or more rings, said rings may each independently bear 0 to 4 substituents independently selected from halo, hydroxy, cyano, nitro, oxo, thio, aminosulfonyl, phenyl, phe-

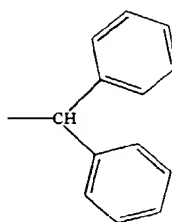
noxy, phenylthio, halophenylthio, benzyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₁₀)alkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylamino(C₁-C₁₀)alkoxy, (C₁-C₃)perfluoroalkyl, (C₁-C₃)perfluoroalkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)acyloxy, (C₁-C₁₀)acyloxy(C₁-C₁₀)alkyl, and pyrrolidinyl; or

G, wherein G is selected from the group consisting of:

(a) a phenyl or heterocyclic ring wherein said heterocyclic ring contains a total of from 3 to 14 ring atoms, wherein said heterocyclic ring incorporates a total of from 1 to 4 ring heteroatoms selected independently from oxygen, nitrogen, and sulfur, wherein the individual rings of said heterocyclic ring may be independently saturated, partially saturated or aromatic, and wherein each of said phenyl or heterocyclic rings may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thio, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acyloxy, (C₁-C₆)acylamino and (C₁-C₆)perfluoroacylamino;

(b) -CH₂CN,

(c)



(d) (C₂-C₁₂)alkyl or (C₂-C₁₂)perfluoroalkyl wherein each of said (C₂-C₁₂)alkyl and (C₂-C₁₂)perfluoroalkyl is substituted optionally with from 1-3 substituents selected independently from:

(1) phenyl, halogen, nitro, cyano, hydroxy, -NR¹R², -OCOR³, (C₁-C₄)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)thioalkoxy or (C₁-C₄)perfluorothioalkoxy,

where R¹ and R² in the definition of -NR¹R² are each selected independently from hydrogen, formyl, phenyl, benzyl, benzoyl, (C₃-C₈)cycloalkyl, (C₃-C₈)cycloalkenyl, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₆)acyl, (C₁-C₆)perfluoroacyl, aminocarbonyl, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, aminosulfonyl, (C₁-C₄)alkylaminosulfonyl, di(C₁-C₄)alkylaminosulfonyl, (C₁-C₄)perfluoroalkylaminosulfonyl, di(C₁-C₄)perfluoroalkylaminosulfonyl, (C₁-C₄)alkylsulfonyl, and (C₁-C₄)perfluoroalkylsulfonyl,

or where R¹ and R², taken together with the nitrogen atom to which they are attached, form a saturated, partially-saturated or aromatic heterocyclic ring, wherein said heterocyclic ring contains a total of from 3 to 14 ring atoms and incorporates optionally an additional 1 to 4 ring heteroatoms selected independently from oxygen, nitrogen and sulfur, wherein said heterocyclic ring may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thio, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acylamino, and (C₁-C₁₀)acyloxy,

where R³ in the definition of -OCOR³ is selected from -NR¹R², phenyl, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₆)alkoxy and (C₁-C₆)perfluoroalkoxy,

(2) (C₃-C₈)cycloalkyl or (C₃-C₈)cycloalkenyl wherein each of said (C₃-C₈)cycloalkyl and (C₃-C₈)cycloalkenyl may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thio, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylami-

nocarbonyl,

di(C₁-C₁₀)alkylaminocarbonyl, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acylamino, (C₁-C₁₀)perfluoroacylamino, (C₁-C₁₀)acyloxy, and

(3) a saturated, partially-saturated or aromatic heterocyclic ring containing a total of from 3 to 14 ring atoms, wherein said heterocyclic ring incorporates a total of from 1 to 4 ring heteroatoms selected independently from oxygen, nitrogen and sulfur, wherein said heterocyclic ring may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acylamino, (C₁-C₁₀)perfluoroacylamino, (C₁-C₁₀)acyloxy;

(e) (C₃-C₈)cycloalkyl or (C₃-C₈)cycloalkenyl wherein each of said (C₃-C₈)cycloalkyl and (C₃-C₈)cycloalkenyl may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acylamino, (C₁-C₁₀)perfluoroacylamino, (C₁-C₁₀)acyloxy; and

(f) -(CH₂)_nCOR⁴, where R⁴ in the definition of -(CH₂)_nCOR⁴ is selected from hydroxy, phenyl, -NR¹R², (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₄)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₃-C₈)cycloalkyl, and (C₃-C₈)cycloalkenyl, where n is an integer from 1 to 4;

(ii) the compound 9-[4-[4-(2,3-dihydro-1-oxo-1 H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof;

(iii) the compound 2-[1-(3,3-diphenylpropyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one, and the pharmaceutically acceptable salts thereof; and

(iv) the compound 9-[4-(4-[2-(4-trifluoromethylphenyl)benzoylamino]piperidin-1-yl)butyl]-N-2,2,2-trifluoroethyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof.; and

said anti-obesity agent is selected from the group consisting of a β₃-adrenergic receptor agonist, a cholecystokinin-A agonist, a monoamine reuptake inhibitor, a sympathomimetic agent, a serotonergic agent, a dopamine agonist, a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone receptor analog, a cannabinoid receptor antagonist, a melanin concentrating hormone antagonist, leptin, a leptin analog, a leptin receptor agonist, a galanin antagonist, a lipase inhibitor, a bombesin agonist, a Neuropeptide-Y antagonist, a thyromimetic agent, dehydroepiandrosterone or an analog thereof, a glucocorticoid receptor agonist or antagonist, an orexin receptor antagonist, a urocortin binding protein antagonist, a glucagon-like peptide-1 receptor agonist, a ciliary neurotrophic factor, and a human agouti-related protein antagonist.

14. A composition according to claim 13 wherein said apo B secretion/microsomal triglyceride transfer protein inhibitor is a compound selected from the group consisting of:

4'-trifluoromethyl-biphenyl-2-carboxylic acid-(2-butyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide, the hydrates thereof, and the pharmaceutically acceptable salts of said compound and said hydrates;

4'-trifluoromethyl-biphenyl-2-carboxylic acid-[2-(2-acetylminoethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]amide, the hydrates thereof, and the pharmaceutically acceptable salts of said compound and said hydrates; 9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof;

2-[1-(3,3-diphenylpropyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one, and the pharmaceutically acceptable salts thereof; and

9-[4-(4-[2-(4-trifluoromethylphenyl)benzoylamino]piperidin-1-yl)butyl]-N-2,2,2-trifluoroethyl-9H-fluorene-9-carboxamide, and the pharmaceutically acceptable salts thereof; and

said anti-obesity agent is a compound selected from the group consisting of sibutramine, orlistat, fenfluramine, dexfenfluramine, bromocriptine, phentermine, ephedrine, leptin, phenylpropanolamine, pseudoephedrine, {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenyl}acetic acid, {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenyl}benzoic acid, {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenyl}propionic acid and {4-[2-(2-[6-aminopyridin-3-yl]-2(R)-hydroxyethylamino)ethoxy]phenoxy}acetic acid.

15. A method of reducing intestinal fat absorption in an animal which comprises administering to an animal in need of such reduction an intestinal fat absorption reducing amount of a composition of claim 11.

5 16. A kit comprising an amount of an apolipoprotein B secretion/microsomal triglyceride transfer protein inhibitor and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form; an amount of an anti-obesity agent and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and a container.

10

15

20

25

30

35

40

45

50

55

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 1 099 439 A3

(12)

EUROPEAN PATENT APPLICATION

(88) Date of publication A3:
26.03.2003 Bulletin 2003/13

(43) Date of publication A2:
16.05.2001 Bulletin 2001/20

(21) Application number: **00309721.9**

(22) Date of filing: **03.11.2000**

(51) Int Cl.⁷: **A61K 31/00**, A61K 31/472,
A61K 31/454, A61K 31/4468,
A61P 3/04
// (A61K31/472, 31:00),
(A61K31/454, 31:00),
(A61K31/4468, 31:00)

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR**
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **10.11.1999 US 164547**

(71) Applicant: **Pfizer Products Inc.
Groton, Connecticut 06340 (US)**

(72) Inventors:
• **Chandler, Charles Edward
Kula, Maui, Hawaii 96790 (US)**

• **Hickman, Mary Anne
Groton, Connecticut 06340 (US)**
• **Lundy, Kristin Marie
Groton, Connecticut 06340 (US)**
• **Morgan, Bradley Paul
Groton, Connecticut 06340 (US)**

(74) Representative:
**Atkinson, Jonathan David Mark et al
Urquhart-Dykes & Lord
Tower House
Merrion Way
Leeds LS2 8PA (GB)**

(54) **Use of apo B secretion/MTP inhibitors**

(57) The invention provides methods useful in reducing intestinal fat absorption in an animal, preferably a mammal including a human subject or a companion animal, which methods comprise administering to an animal in need of such reduction, an amount of an apolipoprotein B (apo B) secretion/microsomal triglyceride transfer protein (MTP) inhibitor, preferably in combination with an anti-obesity agent. The invention further provides pharmaceutical compositions comprising amounts of an apo B secretion/MTP inhibitor and an anti-obesity agent, and to methods of using such compo-

sitions in reducing intestinal fat absorption in an animal, preferably a mammal including a human subject or a companion animal, in need of such reduction. The invention further provides a kit comprising an amount of an apolipoprotein B secretion/microsomal triglyceride transfer protein inhibitor and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form; an amount of an anti-obesity agent and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and a container.

EP 1 099 439 A3



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

EP 00 30 9721

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (InCL7)
X	WO 96 40640 A (QUALLICH GEORGE J ;DORFF PETER H (US); CHANG GEORGE (US); PFIZER ()) 19 December 1996 (1996-12-19) * page 1 * * claims 1,2,30,31 *	1,2,4,5, 11,12, 15,16	A61K31/00 A61K31/472 A61K31/454 A61K31/4468 A61P3/04 //(A61K31/472, 31:00), (A61K31/454, 31:00), (A61K31/4468, 31:00)
X	WO 97 41111 A (PFIZER ;URBAN FRANK JOHN (US)) 6 November 1997 (1997-11-06) * page 11, paragraph 2 - paragraph 3 * * page 13, paragraph 2 *	1,2,4,5, 11,12, 15,16	
X	WO 98 23593 A (CHANG GEORGE ;PFIZER (US); QUALLICH GEORGE JOSEPH (US)) 4 June 1998 (1998-06-04) * page 13, line 28 - page 17, line 22 * * page 57; example 6 * * page 60; example 6 * * claims 1,42-48 *	1-6,11, 12,15,16	
X	EP 0 887 345 A (PFIZER) 30 December 1998 (1998-12-30) * examples 5-8 * * page 6, line 16 - line 22 *	1-3	TECHNICAL FIELDS SEARCHED (Int.Cl.7) A61K
-/-			
INCOMPLETE SEARCH <p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search: see sheet C</p>			
Place of search THE HAGUE		Date of completion of the search 29 January 2003	Examiner Bonzano, C
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

EPO FORM 1503 (3.82) (P04007)



European Patent
Office

INCOMPLETE SEARCH
SHEET C

Application Number
EP 00 30 9721

Although claims 1-10,15 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Claim(s) searched completely:

14

Claim(s) searched incompletely:

1-13,15,16

Reason for the limitation of the search:

Present claims 1,4-13,15,16 relate to compounds defined by reference to a desirable pharmacological property, namely the activity as apolipoprotein B secretion/microsomal triglyceride transfer protein inhibitor, as antiobesity agent, as adrenergic receptor agonist, cholecystokinin agonist, MAO inhibitor, sympathomimetic agent, serotonergic agent, dopamine agonist, melanocyte-stimulating hormone receptor agonist or mimetic, melanocyte-stimulating hormone receptor analog, cannabinoidreceptor antagonist, melanin concentrating hormone antagonist, leptin, leptin analog/agonist, galanin antagonist, lipase inhibitor, bombesin antagonist, neuropeptide y antagonist, thyromimetic agent, analogs of dehydroepiandrosterone, glucocorticoid receptor agonist or antagonist, orexin receptor antagonist, urocortin binding protein antagonist, glucagon-like peptide 1 receptor agonist, ciliary neurotrophic factor, human agouti-related protein antagonist.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 83 EPC and disclosure within the meaning of Article 84 EPC for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure.

Moreover, the terms above mentioned are vague and unclear and leave the reader in doubt as to the meaning of the effective compounds to which they refer, thereby rendering the definition of the subject-matter of said claims unclear (Article 84 EPC).

Claims 1-10,15 relate to therapeutic applications which are actually not well defined. The use of the definitions "reducing intestinal fat absorption" in the present context is considered to lead to a lack of clarity within the meaning of Article 84 EPC.

Present claims 2,5,13 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables and possible permutations, that a lack of clarity (and conciseness) within the meaning of Article 84 EPC arises. Moreover, it is not clear whether the "G" group in claim 2, page 28, is a substituent of Z or a definition of L. The "G" group, consequently, has been ignored for the search.

This lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds structurally identified in claims 3, 6, 8-10,14 in the treatment of obesity, and in the reduction of serum fats.



European Patent
Office

**INCOMPLETE SEARCH
SHEET C**

Application Number
EP 00 30 9721

with due regard to the general idea underlying the present invention.



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 00 30 9721

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	DATABASE WPI Section Ch, Week 200036 Derwent Publications Ltd., London, GB; Class B05, AN 2000-412601 XP002198608 & JP 2000 169395 A (PFIZER PROD INC), 20 June 2000 (2000-06-20) * abstract *	1-3	
X	US 5 474 993 A (RUBIN BYRON ET AL) 12 December 1995 (1995-12-12) * page 18, line 1 - line 15 *	1	
X	EP 0 584 446 A (SQUIBB & SONS INC) 2 March 1994 (1994-03-02) * page 18, paragraph 1 - paragraph 3 *	1	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	VISIOLI F.: "Microsomal triglyceride transfer protein inhibitors." CURRENT OPINION IN CARDIOVASCULAR, PULMONARY AND RENAL INVESTIGATIONAL DRUGS, (2000) 2/3 (292-293). XP008002917 * page 292, column 1, paragraph 1 - paragraph 2 *	1-3	
X	FUNATSU, T. ET AL: "Prolonged inhibition of cholesterol synthesis by atorvastatin inhibits ap B-100 and triglyceride secretion from HepG2 cells" ATHEROSCLEROSIS (SHANNON, IRELAND) (2001), 157(1), 107-115, XP001075042 * page 108, column 1, paragraph 2 - paragraph 3 *	1-3	
	-/-		

EPO FORM 1803 (6.8.92) (p.4/19)



European Patent
Office

Application Number
EP 00 30 9721

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

- ☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- ☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

PARTIAL EUROPEAN SEARCH REPORT

EPO FORM - 503 03.82 (P04C10)

7



European Patent
Office

**LACK OF UNITY OF INVENTION
SHEET B**

Application Number
EP 00 30 9721

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 1-16 (partially)

Use of compounds of formula I alone or in combination with anti obesity agents, for reducing intestinal fat absorption.

2. Claims: 1-16 (partially)

Use of the compounds BMS197636 or BMS 201038 alone or in combination with antiobesity agents for reducing fat absorption.

3. Claims: 1-16 (partially)

Use of the compound BMS 200150 alone or in combination with antiobesity agents for reducing fat absorption.